REMARKS

Claims 16-30 and 32-34 presently appear in this case. No claims have been allowed. The official action of February 16, 2005, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method of treating host vs. graft disease (HVGD), i.e., graft or transplant rejection, by administering Copolymer 1 or a Copolymer 1-related random copolymer to a mammal that is a transplant recipient.

Claims 16-30 and 32-34 have been rejected under 35 U.S.C. §101 because the claimed invention is supported by a well-established utility. The examiner states that the claims recite that HVGD can be prevented although there is no evidence that this is the case. The examiner suggests that the term "preventing" be deleted from the claims. Claims 16-30 and 32-34 have also been rejected under 35 U.S.C. §112, first paragraph, for the same reasons. These rejections are respectfully traversed.

Claim 16 has now been amended to change the term "preventing" to read "suppressing". This language is supported, for example, by the paragraph bridging pages 17 and 18 of the present specification. Note particularly in this paragraph where it states, "... Copolymer 1 is effective in

suppressing in mice the rejection of grafts .... Thus, graft rejection could be suppressed .... Moreover, Copolymer 1 is also effective in suppressing in mice rejection of grafts from strains of different MHC haplotypes ...."

The term "suppression" does not imply that not even a single test subject exhibits any symptoms of the disease at all. However, it does leave open the possibility that the disease is completely avoided in any given case. Accordingly, it is believed that this amendment eliminates the objection noted by the examiner. Reconsideration and withdrawal of these rejections are therefore respectfully urged.

Claims 16-30 and 32-34 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner states that applicants have shown that copolymer 1 can be used to treat GVHD but copolymer 1 is excluded from the claims, and thus none of the compounds within the claimed genus has been tested in any assay. This rejection is respectfully traversed.

The present claims have now been amended to delete reference to the non-elected embodiment of treatment of GVHD. Accordingly, this part of the rejection has now been obviated.

Claims 19, 20, 25, 27, 29 and 34 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that the term "about" in reference to a

range renders the claims indefinite as to the upper and lower limits. This rejection is respectfully traversed.

The examiner's attention is invited to MPEP §2173.05(b), where it states that the fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. §112, second paragraph. Specifically, with respect to the term "about", the MPEP states at page 2100-209 (Rev. 2, May 2004):

> The term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was held to be clear, but flexible. *Ex parte Eastwood*, 163 USPQ 316 (Bd. App. 168). Similarly, in *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as "exceeding about 10% per second" is definite because infringement could clearly be assessed through the use of a stopwatch.

Here, there is no close prior art, and accordingly, there is no reason to believe that this terminology would be considered to be indefinite. Just as the term "about" was used in a range in *Ex parte Eastwood* and found to be definite and cited with approval in the MPEP, so the examiner should allow the clear but flexible language of the present claims for the same reasons. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claim 16 has been rejected under 35 U.S.C. §102(e) as being anticipated by Jameson. The examiner states that Jameson discloses various peptides that are useful to treat GVHD and transplantation rejection, and among these is SEQ ID NO:17, which includes amino acids Cys, Glu, Leu, Asn, Arg, Lys, Val, Trp, Phe and Thr. The examiner states that because the peptide contains Glu, Arg, Trp and Lys, it meets the amino acid composition requirements. This rejection is respectfully traversed.

Claim 16 has now been amended to specify that the active ingredient is a random copolymer consisting of amino acid residues selected from the group consisting of one amino acid from at least three of the four groups specified in the claim. Thus, the claim language no longer reads on all possible peptide sequences that include at least one Glu, Arg, Trp and Lys. The claim now uses closed language to ensure that only the specified three or four amino acids are present. That Copolymer 1 is a copolymer consisting of only four residues is clear from the present specification, for example, at page 3, lines 5-17, and particularly line 6. As this concept is supported in the specification, this revised language does not contain any new matter. As the present language of claim 16 excludes the presence of Cys, Asn, Val,

Thr, etc., Jameson does not anticipate. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claim 16 has been rejected under 35 U.S.C. §103 as being unpatentable over Aharoni. The examiner states that Aharoni discloses Copolymer 1 and compositions containing it. The examiner states that the disclosed peptide could be used to treat host vs. graft disease other than graft vs. host disease and that it would be obvious to one of ordinary skill in the art that a compound that is effective to treat GVHD will be effective to treat HVGD. Further, the examiner states that it would be obvious to use a modification of Copolymer 1 for treatment of GVHD as is encompassed by the claims. This rejection is respectfully traversed.

Claim 16 has now been amended so as to only be directed to the treatment of host vs. graft disease, i.e., transplant rejection. Aharoni teaches that Copolymer 1 is useful for the treatment of graft vs. host disease. However, there is no mention that Copolymer 1 would be useful for the treatment of HVGD or transplantation rejection. Contrary to the examiner's unsupported statement, there is no reason to believe that it would have been obvious that a treatment that is effective for the treatment of GVHD would be effective to treat transplantation rejection.

Graft versus host disease and graft rejection are both pathological situations in which the immune system manifests a detrimental activity. However diversification among immunological disorders does exist, and the above two situations comprise distinct and totally different phenomena as detailed in the following.

Graft versus host disease is manifested only in the restricted population of bone marrow transplanted patients who had been totally immunosuppresed prior to transplantation, and is characterized by the reactivity of the donor transplanted T-cells against the immuno-incompetent host (Ferrara et al, "The pathophysiology of acute graft-versus-host disease", Int Hematol 78(3):181-187 (2003); P. Reddy, "Pathophsiology of acute graft-versus-host disease", Hematol Oncol 1294):146-141 (2003)). The conditioning regimen (high-dose chemo/radiotherapy) is a major trigger of this disease, leading to tissue damage, secretion of inflammatory cytokines, and induction of MHC as well as adhesion molecules. This activation results in enhanced recognition of host antigens by the donor T-cells that proliferate, secrete inflammatory cytokines, and recruit additional effector cell populations (natural killer and cytotoxic cells). Yet, GVHD is considered as being primarily mediated by detrimental cytokines ("cytokine storm") such as TNF-α and IFN-γ (Krenger et al,

"Dysregulation of cytokines during graft-versus-host disease", J. Hematother 5(1):3-14 (1996)). Further amplification of the symptoms is caused by endotoxins that leak across the damaged gastrointestinal mucosa resulting in a vicious pathological feedback loop. As a result, GVHD is a severe systemic disease in which various organs and tissues such as the skin and the gastrointestinal system are affected, in some cases leading to complete failure of various organs and eventually death.

Organ/graft rejection (a situation which is termed host-versus-graft response, or HVGD) occurs in immunocompetent hosts and is defined by the reactivity of the transplanted patients to the specific organ or tissue grafted in them (Pattison et al, "New insights into mechanisms of allograft rejection", Am J Med Sci 313(5):257-263 (1997); MM Aw, "Transplant immunology", J Pediatr Surg 38(9):1275-1280 (2003)). Hence, the host recognizes the alloantigens in the transplanted organ/tissue as non-self and attacks them. The bulk of evidence points to cytotoxic T-cells as playing the major and crucial role in graft rejection (D. Mason, "The role of T cell subpopulations in allograft rejection", Transplant Proc 20(2):239-242 (1998)). Yet, the "classical" collaborative interaction between class II restricted CD4+, and class I restricted CD8+ cells that differentiate into cytotoxic effector cells, is apparently not an obligatory

requirement in cases of strong allograft responses. All pathological processes in this disorder are specifically aimed at the transplanted organ, leading to deterioration in its function and eventually complete rejection without general systemic damage.

Some treatments of these two syndromes, as well as of other immunological and autoimmune disorders, are similar, aiming at blocking the detrimental reactivity of the immune system by non-specific immunosuppressive drugs. But since these are distinct disorders, other treatments are currently practiced, aimed at the individual mechanisms and stages of each disease. Thus, the most prevalent and effective method to prevent GVHD is the depletion of donor T-cells from the graft, a treatment that is inapplicable for and will not prevent organ rejection. GVHD therapies include also antibiotics, LPS blockage and Thalidomide (Davies et al, "New advance in acute graft-versus-host disease prophylaxis", Transfus Med 13(6):387-397 (2003); Nesca et al, "Dermathologic and nondermathologic uses of thalidomide", Ann. Parmacother 37(9):1307-1320 (2003)). In contrast, therapies against graft rejection include a mosaic of immunosuppressive drugs and mycophenolate mofetil (MMF cellsept) (Ma et al, Small molecule immunosuppressive agents in experimental and clinical transplantation", Curr Drug Targets Cardiovasc Haematol Disord

2(2):57-71 (2002); MA Masri, "The mosaic of immunosuppressive drugs", Mol Immunol 39:1073-1077 (2003)).

In summary, GVHD and graft rejection are two distinct disorders. Induction of a certain treatment for one of them does not apply for treating the other disorder, just as it does not allow the treatment of any other disease in which the immune system is involved (e.g., autoimmune diseases). Hence, distinct and independent patenting procedures for each one of them are essential.

It is important to emphasize that even in the case of different autoimmune diseases, which have much more in common to each other than GVHD and host versus graft rejection, individual therapies merit distinct patents. Hence, the previous patent regarding GVHD from the laboratory of the present inventors definitely does not reduce the novelty of the present application. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 16 and 17 have been rejected under 35 U.S.C. §103 as being unpatentable over Leto. The peptide of Leto includes amino acids such as Thr, Ser, Pro and Val. The examiner states that this peptide can be used to treat tissue transplant rejection and tissue graft rejection. This rejection is respectfully traversed.

As indicated above, claim 16 has now been amended so as to define the random copolymer so as to exclude anything except the three or four amino acids specified. As the peptide of Leto has many other amino acids, it is not a random copolymer in accordance with the definition in the claims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claim 16 has been rejected under 35 U.S.C. §103 as unpatentable over Jameson, and claim 16 has also been rejected under 35 U.S.C. §103 as unpatentable over Clayberger. The examiner states that each of these references includes peptides for treating organ transplant rejection that have the requisite amino acids. These rejections are respectfully traversed.

As with the other peptides discussed above, the peptides of Jameson and Clayberger include amino acids other than those to which the random copolymers are restricted in the present claims. It would not be obvious to omit them. Accordingly, the present claims are not anticipated or made obvious by these references. Reconsideration and withdrawal of these rejections are therefore also respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and

fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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